IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	)	Group Art Unit: 1633
	)	
Kyuhyun LEE et al.	)	Examiner: HIRIYANNA, KELAGINAMANE T
	)	
Serial No.: 10/584,383	)	Confirmation No.: 3667
	)	
Filed: 06/26/2006	)	
	)	
For: THERAPEUTIC AGENT FOR TREATMENT OF CANCER COMPRISING HUMAN APOLIPOPROTEIN (A) KRINGLES LK68 OR LK8 GENES AS EFFECTIVE INGREDIENT, AND METHOD FOR TREATING CANCER USING THE SAME	)	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION SUBMITTED UNDER 37 C.F.R. § 1.132

Sir:

I, Eui-Cheol Jo of MOGAM Biotechnology Research Institute, do hereby declare the following:

1. I am a Research Fellow in the department of Biomedical Engineering Division at MOGAM Biotechnology Research Institute.

2. As attested by my *curriculum vitae* attached hereto, I am knowledgeable and skilled in the field of genetic diagnosis, especially with respect to cancer diagnostic marker.

3. I am an inventor in the above-identified application, serial number: 10/584,383.

4. I have read and understand the subject matter of the above-identified application, the Office Action mailed January 24, 2007, and the claims filed with this Declaration as well as the claims as previously presented.

5. The following are my comments offered in support of the patentability of the instant invention, particularly, in connection with the alleged rejection under 35 USC 35 U.S.C. §112, first paragraph, on pages 2-6 of the Office Action mailed January 24, 2007. The comments also referred to Figures 1 and 2 attached to this Declaration.

< Experimental Procedures and Results >

Example 1: Histological analysis of anti-angiogenic activity

The Matrigel plug assay was performed as follows to test anti-angiogenic activity of LK8 and LK68. First, Matrigel plug was transferred to mice. Second, pDNAs, including pcDNA/LK8, pcDNA/LK68, pAAV-CMV/LK8, and pAAV-CMV/LK68, were administered to the mice to express LK8 and LK68. Thereafter, angiogenesis was assessed by scoring selected regions of histological sections for vascular density.

Figure 1 shows angiogenesis in Matrigel when LK8 and LK68 were expressed from pcDNA/LK8, pcDNA/LK68, pAAV-CMV/LK8, and pAAV-CMV/LK68. The level of angiogenesis in Matrigel was observed at 40X and 100X by optical microscopy. The results indicate that the level of anti-angiogenic activity was higher in samples with pAAV-CMV/LK8 and pAAV-CMV/LK68 compared with pcDNA/LK8 and pcDNA/LK68. However, and compared to control experiments in which only saline was administered, the samples with pcDNA/LK8 and pcDNA/LK68 still showed anti-angiogenic activity.

Example 2: Hemoglobin analysis of anti-angiogenic activity

The Matrigel plug assay was performed as described above and formation of new blood vessels was analyzed.

Figure 2 shows the degree of anti-angiogenesis in Matrigel when LK8 and LK68 were expressed from pcDNA/LK8, pcDNA/LK68, pAAV-CMV/LK8, and pAAV-CMV/LK68. The level of angiogenesis in Matrigel was measured by hemoglobin assay. The results indicate that the level of anti-angiogenic activity was higher in samples with pAAV-CMV/LK8 and pAAV-CMV/LK68 compared with pcDNA/LK8 and pcDNA/LK68 samples. However, compared to the control in which only saline was administered, the samples with pcDNA/LK8 and pcDNA/LK68 still showed anti-angiogenic activity.

6. I conclude that the above described experiments and data provided in Figures 1 and 2 are consistent with the disclosure in the above-identified patent application (10/584,383). The experiments and data are representative examples of using gene carriers containing LK68 or LK8 genes as disclosed in the application. These representative examples provide evidence to a skilled person or artisan that any gene carrier known in the art, harboring and expressing LK68 or LK8 gene, may be used as disclosed to treat a solid tumor or its metastasis. The above-described experimental data from animals indicate that AAV viral vectors and other plasmid vectors, as exemplified by pcDNA/LK8 and pcDNA/LK68, may be used to express LK68 or LK8 to treat a solid tumor or its metastasis.

7. The undersigned hereby declares that all statements made herein based upon knowledge are true, and that all statements made based upon information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section

1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

DATED: June 19, 2009

Name: Eui-Cheol Jo

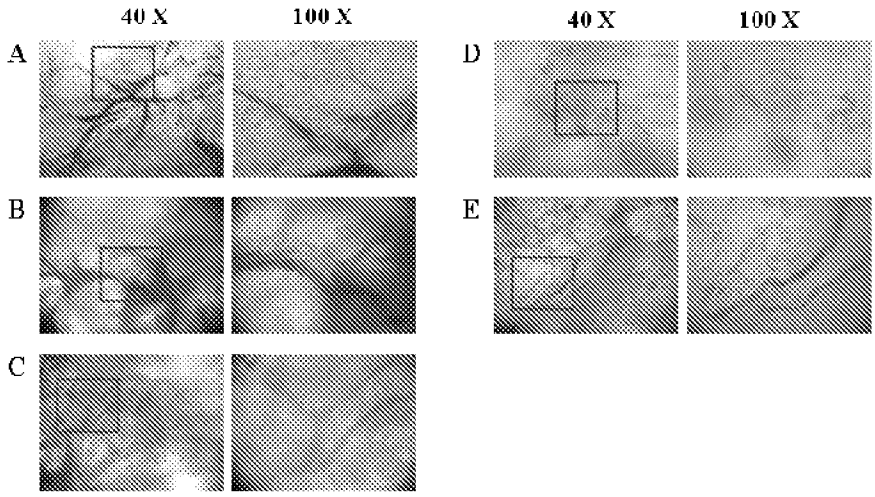

FIG. 1 A. control (saline), B. pcDNA/LK8, C. pcDNA/LK68, D. pAAV-CMV/LK8, and E. pAAV-CMV/LK68

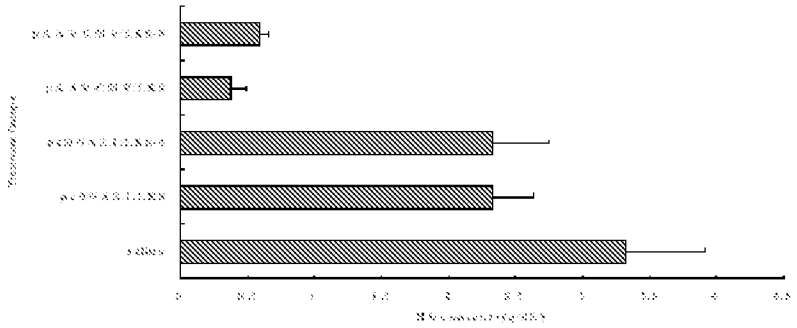

FIG. 2

CURRICULUM VITAE

MOGAM BIOTECHNOLOGY RESEARCH INSTITUTE

Limited use only to endorse "Declaration submitted under 37 C.F.R. §1.132 to US PTO" in association with the patent application serial no. 10/584,383
June 18, 2007

BIOGRAPHYCIAL

Name: Eui-Cheol Jo

Business Address: Biomolecular Engineering Division
341 Pojung-Dong Kiheung-Ku Yongin Kyonggi-Do 446-799, Korea
ecjo@mogam.re.kr

Business Phone: +82 31 260 9849 Business Fax: +82 31 260 9808

POSITION

Research Fellow, MOGAM Biotechnology Research Institute	2006 - Present
Chief Scientist	2001 - 2005
Principal Research Scientist	1994 - 2000
Senior Research Scientist	1987 - 1994
Research Scientist	1984 - 1987

EDUCATION

UNDERGRADUATE

B. S. Department of Food Engineering, College of Engineering, Yonsei University — February 1983

Dissertation: *Rheological Characterization of the Rice Starch*

GRADUATE

M. S. Department of Biological Science and Engineering February 1985

Korea Advanced Institute of Science and Technology (KAIST)

Dissertation:

Enhancement of Productivity by Air-Supplement in Immobilized Cell Reactor for Ethanol Productivity

Ph.D. Department of Biological Science February 1998

Korea Advanced Institute of Science and Technology (KAIST)

Dissertation:

Development of perfusion culture system of recombinant CHO cells for the production of urokinase-type Plasminogen Activator

Reference

Professor Jung Hoe Kim

Department of Biological Science

Korea Advanced Institute of Science and Technology (KAIST)

373-1 Eoun-Dong Yusong-Ku, Taejun 305-701, Republic of Korea

Tel: +82 42 869 2614 e-mail: kimjh@kaist.ac.kr

MEMBERSHIP IN PROFESSIONAL AND SCIENTIFIC SOCIETIES

The Korean Society for Microbiology and Biotechnology

The Korean Society for Biotechnology and Bioengineering

Korean Institute of Chemical Engineers; Biochemical Engineering Division

Korean Society of Gene Therapy

Korean Society for Molecular and Cellular Biology

American Chemical Society (1993-2006)

The European Society for Animal Cell Technology

American Society of Gene Therapy

American Society for Biochemistry and Molecular Biology

The International Society for Protein Expression

HONORS AND AWARDS

Registered in,

The Marquis' Who's Who in the World (1995-Present)

The Marquis' Who's Who in Science and Engineering

The Marquis' Who's Who in Finance and Industry

FIELD OF CURRENT RESEARCH INTEREST

Biochemical Engineering/Mammalian Cell Culture

Therapeutics for Cardiovascular Disease and Cancer

Gene Therapy: Genetic Diseases, Oncology, Vector Production Process

RESEARCH RELATED ACTIVITIES

Member of Editorial Board: *Biotechnology and Bioprocess Engineering*

Review for: *Biotechnology and Bioengineering*

Nucleic Acids Research (2004)

Biotechnology Progress (2005, 2007)

Hepatology (2006)

Journal of Cancer Research and Clinical Oncology (2006)

PUBLICATIONS

1. *Kyuhyun Lee, Sung-Tae Yun, Young-Gun Kim, Yeup Yoon, and* ***Eui-Cheol Jo*** (2006) Adeno-associated virus-mediated expression of apolipoprotein (a) kringles suppresses hepatocellular carcinoma growth in mice. *Hepatology* 43(5): 1063-1073.

2. *Joon Young Park, Byung-Pil Lim, Kyuhyun Lee, Young-Gun Kim,* ***Eui-Cheol Jo*** (2006) Scalable production of adeno-associated virus type 2 vectors via suspension transfection. *Biotechnol. Bioeng.* 94(3): 416-430.

3. *Jung-Seob Kim, Byung-Chul Ahn, Byung-Pil Lim, Yang Do Choi and* ***Eui-Cheol Jo***(2004) High-level scu-PA production by butyrate-treated serum-free culture of recombinant CHO cell line. *Biotechnol. Prog.* 20(6): 1788-1796.

4. *Min Tae Park, Myung Seop Lee, Sung Hyun Kim,* ***Eui-Cheol Jo*** *and Gyun Min Lee* (2004) Influence of culture passages on growth kinetics and adenovirus vector production for gene therapy in monolayer and suspension cultures of HEK293 cells. *Appl. Microbiol. Biotechnol.* 65(5): 553-558.

5. *Kyuhyun Lee, Young-Gun Kim and* ***Eui-Cheol Jo*** (2003) Shuttle PCR-based cloning of the infectious adeno-associated virus type 5 genome. *J. Virol. Methods* 111(2): 75-84.

6. *Jung-Seob Kim, Mi-Kyung Min and* ***Eui-Cheol Jo*** (2001) High-level expression and characterization of single chain urokinase-type Plasminogen Activator (scu-PA) produced in recombinant Chinese Hamster Ovary (CHO) cells. *Biotechnol. Bioprocess Eng.* 6(2): 117-127.

7. ***Eui-Cheol Jo****, Jung-Won Yun, Kyung-Hwan Jung, Soo Il Chung and Jung-Hoe Kim* (1998) Performance study of perfusion cultures for the production of single-chain urokinase-type plasminogen activator (scu-PA) in a 2.5 l spin-filter bioreactor. *Bioproess Eng.* 19:363-372.

8. *Bok-Hwan Chun, Song-Yong Park,* ***Eui-Cheol Jo****, Kyung-Hwan Jung, Dong-Il Kim and Hong Mo Moon* (1994) Effect of serum type on hybridoma growth and monoclonal antibody production. *Kor. J. Biotechnol. Bioeng.* 9(3): 253-265.

9. ***Eui-Cheol Jo****, Dong-Il Kim and Hong-Mo Moon* (1993) Step-fortifications of nutrients in mammalian cell culture. *Biotechnol. Bioeng.* 42(10): 1218-1228.

10. ***Eui-Cheol Jo****, Hae-Joon Park, Dong-Il Kim and Hong Mo Moon* (1993) Repeated fed-batch

culture of hybridoma cells in nutrient-fortified high-density medium. *Biotechnol. Bioeng.* 42(10): 1229-1237.

11. ***Eui-Cheol Jo**, Man Bock Gu, Dong-Il Kim and Sung Bok Paik* (1991) Microcarrier culture of BOWES melanoma cells in serum-free medium with human plasma fraction IV-4+V. *Biotechnol. Bioeng.* 38: 247-253.

12. ***Eui-Cheol Jo**, Hae-Joon Park, Jong-Myun Park and Kyong-Ho Kim* (1990) Balanced nutrient fortification enables high-density hybridoma cell culture in batch culture. *Biotechnol. Bioeng.* 36(7): 717-722.

13. *Bok-Hwan Chun, Hye-Sook Kim, **Eui-Cheol Jo**, Song-Yong Park, Dong-Il Kim and Sung-Bok Paik* (1990) Production of human immunodeficiency virus from T-lymphoblastoid cells using serum-free medium. *Biotechnol. Lett.* 12(9): 645-648.

14. *Bok Hwan Chun, **Eui-Cheol Jo** and Dong-Il Kim* (1990) Effect of glucose/glutamine concentrations on hybridoma growth and anti-HBs MAb production in enriched medium. *Kor. J. Biotechnol. Bioeng.* 5(4): 365-371.

15. *Bok-Hwan Chun, **Eui-Cheol Jo**, Dong-Il Kim and Sung-Bok Paik* (1990) Production of anti-hepatitis B surface antigen monoclonal antibody in serum-free medium. *Kor. J. Appl. Microbiol. Bioeng.* 18(2):175-180.

16. *Bok-Hwan Chun, **Eui-Cheol Jo**, Dong-Il Kim and Sung-Bok Paik* (1990) Enhancement of hybridoma cell growth and anti-hepatitis B surface antigen monoclonal antibody production in enriched media with low serum. *Kor. J. Biotechnol. Bioeng.* 5(1):87-94.

17. ***Eui-Cheol Jo**, Chul Kim, Young Jun Kim and Jung-Hoe Kim* (1989) Enhancement of productivity by air-supplement in immobilized cell reactor for ethanol production. *Kor. J. Appl. Microbiol. Bioeng.* 17(2):165-169.

PRESENTATIONS

1. *Kyuhyun Lee, Seong-Tae Yun, Hong-Kyu Lee, and* ***Eui-Cheol Jo*** (2006) Replication deficient adenovirus carrying apolipoprotein(a) kringles suppress tumor growth in NSCLC xenograft tumor model. ASGT 10th Annual Meeting May 31-June 3, 2007, Seattle, WA, USA.

2. *Dae Kyung Koh and* ***Eui-Cheol Jo*** (2007) Hematopoietic diseases and gene therapy: Session I. hemophilia; gene therapy for hemophilia. The First Workshop of Korean Society of Gene Therapy, April 18, 2007, Children's Hospital, School of Medicine, Seoul National University.

3. *Kyuhyun Lee, Seong-Tae Yun, Hong-Kyu Lee, Dae Kyung Koh, and* ***Eui-Cheol Jo*** (2006) Novel anti-angiogenic gene therapy for cancer and cancer metastasis. 2006 KSBB Seoul Symposium: Recent advances in medical application of biotechnology, December 15, 2006, Korea University, Seoul, Korea.

4. *Kyuhyun Lee, Seong-Tae Yun, Hong-Kyu Lee, and* ***Eui-Cheol Jo*** (2006) Gene therapy for colon cancer by adeno-associated viral vector-mediated transfer of apolipoprotein (a) kringles. *Mol. Ther.* 13 (Supplement 1): S361, *ASGT* 9th Annual Meeting May 31-June 4, 2006, Baltimore Convention Center, Baltimore, MD, USA.

5. *Kyuhyun Lee, Seong-Tae Yun, and* ***Eui-Cheol Jo*** (2006) Anti-angiogenic cancer gene therapy with apolipoprotein (a) kringle genes. 2006 International Meeting of *the Microbiological Society of Korea*, EXCO, Daegu, May 4, 2006.

6. *Kyuhyun Lee, Seong-Tae Yun, and* ***Eui-Cheol Jo*** (2005) *In vivo* gene therapy with recombinant adeno-associated virus encoding apolipoprotein (a) kringles suppresses tumor growth and metastasis of colon tumor cells in mice. Annual Meeting of *Korean Society of Medical Biochemistry and Molecular Biology: New Horizons of Biomedical Science*. October 26-27, Seoul KyoYuk MunHwa HoeKwan, Seoul, Korea.

7. *Kyuhyun Lee, Sung-Tae Yun and Eui-Cheol Jo* (2005) Adeno-associated virus-mediated

transfer of the genes encoding cryptic kringle fragments of apolipoprotein (a) suppresses tumor growth and metastasis in vivo. *Mol. Ther.* 11 (Supplement 1): S116, *American Society of Gene Therapy* 8th Annual Meeting, June 1-5, St. Louis, MO, USA.

8. *Joon-Young Park, Kyuhyun Lee, Hong-Kyu Lee, Byoung Pil Lim, and* ***Eui-Cheol Jo*** (2005) Efficient scalable production of adeno-associated virus type 2 vectors. *Asia-Pacific Biochemical Engineering Conference (APBioChEC'05): Biochemical Engineering from Genomics to Human Well-Being*. May 15-19. Lotte Hotel Jeju, Jeju Island, Korea.

9. ***Eui-Cheol Jo*** (2004) Current trend and future prospect of gene therapy industry. International Symposium and Annual Meeting of *Korean Society for Biotechnology and Bioengineering*, October 13-15, Chungbuk National University, Cheongju, Korea.

10. *Kyuhyun Lee, Byoung Pil Lim, Seong-Tae Yun, and* ***Eui-Cheol Jo*** (2004) Adeno-associated virus-mediated transfer of a novel antiangiogenic agent suppresses tumor growth and metastasis in vivo. The 16th Annual Meeting of the *Korean Society for Molecular and Cellular Biology*, October 14-15, Seoul KyoYuk MunHwa HoeKwan, Seoul, Korea.

11. *Joon-Young Park, Byoung Pil Lim, Young-Gun Kim, Kyuhyun Lee, and* ***Eui-Cheol Jo*** (2004) Purification of vectors derived from adeno-associated virus type 2 by using column chromatography. The 16th Annual Meeting of the *Korean Society for Molecular and Cellular Biology*, October 14-15, Seoul KyoYuk MunHwa HoeKwan, Seoul, Korea.

12. *Kyuhyun Lee, Young-Gun Kim, and* ***Eui-Cheol Jo*** (2003) Shuttle PCR-based cloning of the infectious adeno-associated virus type 5 genome. *International Biotechnology Symposium: New Challenges in the Post Genome Era 2003*, November 13-14, Yonsei University, Seoul, Korea.

13. *Joon-Young Park, Byung-Pil Lim, Doo Hong Park and* ***Eui-Cheol Jo*** (2002) Media development for serum-free culture of HEK 293 cells. Annual Meeting of the *Korean Society for Microbiology and Biotechnology*, October 26, KonKuk University, Seoul, Korea.

14. *KyuHyun Lee, Young-Gun Kim and* ***Eui-Cheol Jo*** (2002) Cloning of the infectious adeno-

associated virus type 5 genome by shuttle PCR. The 14th Annual Meeting of the *Korean Society for Molecular and Cellular Biology*, October 17-18, KyoYuk MunHwa HoeKwan, Seoul, Korea.

15. *Myung Seop Lee, Min Tae Park,* ***Eui-Cheol Jo*** *and Gyun Min Lee* (2001) Monolayer and suspension cultures of HEK 293 cells for recombinant adenovirus production for gene therapy: Effect of "cell passage number." Spring Meeting of *Korean Society for Biotechnology and Bioengineering*. Konkuk Univ. Seoul, Korea.

16. ***Eui-Cheol Jo*** (2000) Mammalian cell culture process for the production of the biopharmaceuticals. Spring Meeting of the *Korean Institute of Chemical Engineers* (KiChE), Hanyang University, Ansan, Korea.

17. ***Eui-Cheol Jo****, Kwang-Jong Kim, Kyung-Hwan Jung, Soo-Il Chung and Jung-Hoe Kim* (1997) Production of urokinase-type plasminogen activator with r-CHO cells in serum-free medium. Animal Cell Technology: Basic & Applied Aspects, Proceedings of the Tenth Annual Meeting of *the Japanese Association for Animal Cell Technology*, Nagoya, Japan, November 5-8, 1997 (eds. Y. Kitagawa, T. Matsuda, and S. Iijima) December 1998, Volume 10, 406 pp., Kluwer Academic Publishers, Dordrecht, The Netherlands.

18. *Jae-Hoon Hwang, Joo-Hyung Ahn,* ***Eui-Cheol Jo,*** *Kyung-Hwan Jung, Hong-Mo Moon and Kwang-Hoe Chung* (1995) Pilot scale purification of recombinant Pro-UK using expanded bed adsorption chromatography. Spring meeting of the *Korean Biochemical Society*, Seoul National University, Korea.

19. Joong-Chul Lee, Sung-Jin Kim, Eui-Cheol Jo, Dong-Il Kim, Kyung-Hwan Jung and Hong-Mo Moon (1992) Production of hepatitis B surface antigen including PreS (preS-HBsAg) in fed-batch culture of recombinant yeast. *Proceedings of Asia-Pacific Biochemical Engineering Conference (APBioChEC '92),* pp. 186-188. Yokohama (April 12 - 15), Japan.

20. ***Eui-Cheol Jo*** *and Dong-Il Kim* (1991) Fed-batch hybridoma cell culture by nutrient-fortification. Annual Meeting of the *Korean Society of Biotechnology and Bioengineering,*

Yonsei University, Seoul, May 4.

21. ***Eui-Cheol Jo**, Hae-Joon Park, Jong-Myun Park and Kyong-Ho Kim* (1990) A nutrient fortification approach to the growth limitations of cultured mammalian cells. Proceedings of Asia-Pacific Biochemical Engineering Conference (*APBioChEC '90*), pp. 145-148, Seoul, Korea.

22. *Jung Chul Lee, Man Bock Gu,* ***Eui-Cheol Jo*** *and Dong-Il Kim* (1990) Production of hepatitis B surface antigen from continuous cultures of recombinant *Saccharomyces cerevisiae*. The 35th Annual Meeting of the *Korean Society for Applied Microbiology*.

23. ***Eui-Cheol Jo**, Hae-Joon Park, Jong-Myun Park and Kyong-Ho Kim* (1988) High-density hybridoma cell culture through medium modification in batch. Presented at the Symposium on Industrial Applications of Biotechnology. In: *Recent Progress in Molecular Biology & Genetic Engineering in Korea, Mol. Biol. Genet.* 3(2): 285-294, October 1988.

24. ***Eui-Cheol Jo**, Hae-Joon Park, Jong-Myun Park and Kyong-Ho Kim* (1988) High-density hybridoma cell culture through medium modification in batch. Presented at the Symposium on Industrial Applications of Mammalian Cell Culture. Joint Meeting of the *Korean Society of Biotechnology and Bioengineering,* and the *Korean Institute of Chemical Engineers.*

25. ***Eui-Cheol Jo**, Man Bock Gu and Kyong-Ho Kim* (1987) Microcarrier culture of BOWES melanoma cells in serum-free medium with human plasma fraction IV-4+V. The 32nd Annual Meeting of *the Korean Society for Applied Microbiology*, Jeju University, Jeju, Korea.

26. ***Eui-Cheol Jo**, Chul Kim, Young Joon Kim and Jung-Hoe Kim* (1984) Enhancement of Productivity by air-supplement in immobilized cell reactor for ethanol production. The 29th Annual Meeting of the *Korean Society for Applied Microbiology*.

PATENTS

An inventor of ten individual domestic and foreign patents. I do not list these patents in detail, on a belief that patent listing hardly influences the instant patent application.